The search for optimal anticoagulation therapy in ACS: The gap between clinical trials and current clinical guidelines

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In most cases, acute coronary syndrome (ACS) is triggered by thrombosis after disruption of an atherosclerotic plaque. Rupture of the atheromatous plaque creates a prothrombotic state with the generation of thrombin, which not only converts fibrinogen to fibrin but also is a potent inducer of platelet aggregation. Indeed, a delicate balance exists between clot formation and lysis that determines the extent of thrombus, distal embolisation or progression of vessel stenosis and occlusion.

In the acute phase of ACS, antiplatelet agents (such as aspirin and clopidogrel or another P2Y12 inhibitor like prasugrel or ticagrelor) and parenteral anticoagulants (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux or bivalirudin) are the cornerstone of treatment. However, antithrombotic drugs are also associated to an increased risk of major bleeds. Therefore, it is important to identify the most appropriate adjunctive antithrombotic therapy before, during and after percutaneous coronary intervention (PCI) of ACS to reduce mortality and improve the prognosis of patients.

Thrombin is essential in platelet activation and aggregation and combination with fibrin to form thrombus, hence thrombin in this process makes an imperative target for pharmacotherapy (1, 2). UFH, LMWH and fondaparinux belong to parenteral anticoagulants known as indirect thrombin inhibitors. Direct thrombin inhibitors bind directly to thrombin and prevent fibrin formation, thrombin-mediated activation of factors V, VIII, XI and XIII, and thrombin-induced platelet activation (3). UFH has been the parenteral anticoagulant of choice for patients with ACS but there are several potential limitations, i.e., variable anticoagulant effect or the possibility of induced thrombocytopenia. In contrast, LMWH and fondaparinux produce more predictable anticoagulant response; due to the reduced affinity to plasma proteins.

Amongst the direct thrombin inhibitors, bivalirudin has a near-immediate effect, linear dose response, short half-life (25 minutes), resulting in a predictable anticoagulant effect with less risk for bleeding. Indeed, bivalirudin might provide significant antplatelet action in addition to anticoagulant effects during PCI. Then, Bivalirudin infusion during PCI confers an inhibitory effect on both thrombin- and collagen-mediated platelet activation and reduces thrombin levels (4). This may be even more evident with coadministration of bivalirudin with more potent antiplatelet agents, such as ticagrelor (5).

Several factors should be considered when deciding the optimal pharmacological regimen from ACS. Risk scoring tools (e.g., GRACE and CRUSADE scores) and guidelines could aid physicians in determining risk for death and bleeding. For the management of patients with ST-elevation myocardial infarction (STEMI) 2012 European Society of Cardiology (ESC) (6) and 2013 ACC/AHA guidelines (7) recommended the use of parenteral anticoagulants in primary PCI, but fondaparinux is not recommended for primary PCI because of the risk of catheter thrombosis (8). For management of patients with non-ST-elevation myocardial infarction (NSTEAMI), 2011 ESC guidelines (9) and 2014 AHA/ACC guidelines (10) also recommended anticoagulation for all patients in addition to dual antiplatelet therapy (Class I, Level A). When we compare both American and European recommendations, we could see very similar recommendations and levels of evidence, especially with the use of bivalirudin (►Table 1).

The main clinical trial for Bivalirudin was HORIZONS-AMI (11). This trial compared bivalirudin with UFH (with or without glycoprotein [GP] IIb/IIIa blockers) in STEMI patients undergoing PCI and showed significantly lower all cause mortality and major haemorrhagic complications with bivalirudin, but also highlighted of the increase rates of acute stent thrombosis in bivalirudin arm. Another important trial was the EUROMAX trial (12), which assessed the comparative effectiveness of bivalirudin in prehospital initiation treatment of STEMI. As in the previous trial, there were a significant reduction in major bleeding and bivalirudin reduced the rate of death, but the EUROMAX trial included important features, such as radial access or use of more potent P2Y12 inhibitors prasugrel and ticagrelor. In NSTEMI, the ACUTY trial (13) showed that bivalirudin alone was non-inferior to UFH or enoxaparin while the rate of major bleeding was significantly lower with bivalirudin as in the ISAR-REACT 4 trial (14). All of these clinical trials have shown the value of bivalirudin in reducing bleeding and mortality.

At present, some controversy has arisen in the new 2014 ESC guidelines of myocardial revascularisation (15). In STEMI patients, there is a change in use of bivalirudin recommendation, from Class I Level B to Class Ia Level A. The reason for the change in only two years lies in recent trials comparing bivalirudin with UFH. The
thrombin activity. As well, rates of rupture of bivalirudin infusion due to re- 
ess, there has been an excess of risk for acute stent thrombosis with bival- 

Acute stent thrombosis occurring within the first hours after the abrupt dis- 
ruption of Bivalirudin infusion due to residual thrombin activity. As well, rates of stent thrombosis after 24 hours trended higher in the UFH+GP IIb/IIIa arm. In addition, the asymmetric use of GP IIb/IIIa between bivalirudin and UFH in previous clinical trials may confound thrombotic and bleeding outcomes (17). Recently, Val- 
gimigli et al. presented the MATRIX radial vs femoral program results, whereby MACE, bivalirudin was not statistically su- prior to UFH at 30 days because the higher than expected rate of myocardial in- farction. For secondary endpoints, the su- periority of bivalirudin was in reducing major bleeding and all cause death but definite stent thrombosis was more com- mon with bivalirudin (18).

Given that there are no comparative clinical trials or there are no trials with equal use of GP IIb/IIIa in bivalirudin and UFH arm, there have been different meta-analysis addressing this issue (19). Capod- annno et al. (20) recently performed a re- view of the use of bivalirudin in ACS and emphasised that the safety benefit of bival- irudin vs HNF plus GP IIb/IIIa has been demonstrated in clinical trials; but it comes at the price of a significant increase in life- threatening thrombotic complications. In a meta-analysis of 16 clinical trials with STEMI and NSTEMI patients, Cavender et al. (21) found an increase in the risk of MACE with bivalirudin compared with the UFH arm and an increase in myocardial infarction. Like the HEAT-PPCI trial, the risk of stent thrombosis was higher with bivalirudin than with UFH. In order to assess early stent thrombosis with bivalirudin, Piccolo et al. (8) conducted a meta-analysis of randomised clinical trials and concluded that in patients undergoing PCI, bivalirudin increased the risk of early stent throm- bosis as compared with other parenteral anticoagulants and this risk did not trans- late in higher rates of death and or myocar- dial infarction.

In this issue of Thrombosis and Haemo- stasis a network meta-analysis by Navarese et al. (22) addresses the efficacy and safety of anticoagulant therapy in ACS. They ana- lysed 42 randomised trials, meaning that

| Table 1: Recommendations of clinical guidelines for STEMI and NSTEMI patients. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Bivalirudin     | UFH             | Enoxaparin      | Fondaparinux    |
| STEMI 2012 ESC Guidelines | Bivalirudin is recommended over UFH and GP IIb/IIIa blocker (Class I, Level B) | UFH must be used in patients not receiving bivalirudin/ enoxaparin (Class I, Level C). | Enoxaparin may be preferred over UFH (Class IIb / Level B) | Fondaparinux is not recommended for primary PCI (Class III, Level B) |
| 2013 AHA Guidelines | Bivalirudin with or without prior treatment with UFH is recommended (Class I, Level B) | In patients with STEMI undergoing PCI, UFH with or without GP IIb/IIIa blockers has been administered (Class I, Level B) | Enoxaparin compared with UFH for primary PCI failed to primary endpoint (ATOLL) | Fondaparinux should not be used as the sole anticoagulant in PCI (Class III, Level B) |
| 2014 ESC Revasc. Guidelines | Bivalirudin 0.75 mg/kg i. v. bolus followed by infusion of 1.75 mg/kg/h for up 4 hours after PCI is recommended (Class IIa, Level A) | UFH 70–100 U/kg i. v. bolus when no GP IIb/IIIa inhibitor is planned (Class I, Level C). | Enoxaparin i. v. 0.5 mg/kg with or without GP IIb/IIIa inhibitor (Class IIa, Level B) | Fondaparinux is not recommended because of risk of catheter thrombosis |
| NSTEMI 2011 ESC Guidelines | Bivalirudin plus provisional GP IIb/IIIa receptor inhibitors are recommended as alternative to UFH plus GP IIb/IIIa blockers (Class I, Level B) | If the initial anticoagulant is Fondaparinux, a single bolus of UFH should be added at the time of PCI (Class I, Level B) | Enoxaparin is recommended when fondaparinux is not available (Class I, Level B) | Fondaparinux is recommended as having the most favourable efficacy-safety profile (Class I, Level A) |
| 2014 AHA Guidelines | Bivalirudin is recommended until diagnostic angiography or PCI with only provisional use of GP IIb/IIIa blockers (Class I, Level B) | If PCI is performed while patient is on fondaparinux, another anticoagulant (UFH or Bivalirudin) is recommended (Class I, Level B) | Enoxaparin 1 mg/kg sc every 12 hours continued for the duration of hospitalisation or until PCI is performed (Class I, Level A) | Fondaparinux 2.5 mg/day continued for the duration of hospitalisation until PCI is recommended (Class I, Level B) |
| 2014 ESC Revasc. Guidelines | Bivalirudin is recommended as alternative to UFH plus GP IIb/IIIa receptor inhibitor during PCI (Class I, Level B) | UFH is recommended as anticoagulant for PCI if patients cannot receive bivalirudin (Class I, Level C) | Enoxaparin should be considered as anticoagulant for PCI if patients pre-treated with enoxaparin sc (Class IIa, Level B) | Patients with fondaparinux 2.5 mg daily, single bolus UFH during PCI is recommended (Class I, Level A) |

this is the largest network meta-analysis published to date. They show reduced bleeding risk with bivalirudin at the price of an increased propensity of myocardial infarction and stent thrombosis with no differences in mortality rates. The authors simultaneously analyse both STEMI and NSTEMI patients, but these clinical scenarios should perhaps be addressed individually, as well as the influence of infusion use of GP IIb/IIIa. Thus, it remains necessary to clarify the absolute magnitude of the reduction in bleeding compared with the rate of stent thrombosis further if there is no difference in general mortality.

Nowadays we have different alternatives in anticoagulant therapy for ACS, but these strategies still have not been compared with the current improvement in technique of PCI (radial access) or the use of the most powerful antiplatelet agents (prasugrel or ticagrelor), which could reduce early stent thrombosis. Indeed, potent new antiplatelet drugs show some clear advantages over older agents such as clopidogrel (5, 23, 24, 25). Until multicentre randomised clinical trials are conducted, clinicians should evaluate thrombotic and haemorrhagic risk of each patient according to their associated comorbidities, to select the optimal antithrombotic therapy for such patients.

Conflicts of interest
None declared.

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